GERMAN DEMOCRATIC REPUBLIC
DEPARTMENT FOR INVENTIONS AND PATENTS
PATENT NO. 61 269
Economic Patent
Granted in accordance with § 5, paragraph 1 of the modified law on patenting

Int. Cl.:	C 07 d
Cl.:	12 p, 10/10
Filing No.:	WP 12 p / 125 709
Filing Date:	July 1, 1967
Publication Date:	April 20, 1968

METHOD FOR PRODUCING s-TRIAZOLO(1,5-a)-PYRIMIDINES SUBSTITUTED IN POSITIONS 5 AND 7 BY BASIC GROUPS

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The invention concerns a method for producing s-triazolo(1,5-a)pyrimidines of the general formula I that are substituted in positions 5 and 7 by basic groups, and their salts.

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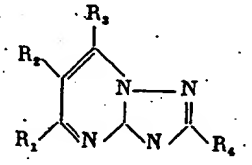


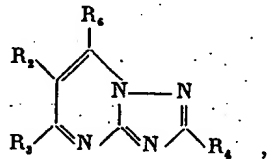
In this formula R_2 and R_4 mean hydrogen atoms, alkyl residues of chain length C_1-C_4, halogen atoms or optionally nucleus-substituted aralkyl-aryl or heterocyclic residues, where R_2 and R_4 do not necessarily have to be the same, R_1 and R_3 mean free amino groups or amino groups substituted by the same or different residues, where these residues mean alkyl, cycloalkyl,

alkenyl, hydroxyalkyl, alkylaminoalkyl, alkyoxy groups, or also optionally substituted hydrazine or guanidine residues, also R_1 and R_3 can be basically substituted alkyl groups with a normal or branched chain of 2-4 carbon atoms, in which the basic residue can carry one of said substituents. R_1 and R_3 do not necessarily have to be the same.

Of the compounds that correspond to general formula I, only 5,7-diamino-s-triazolo(1,5-a)pyrimidine was known up to now ($R_1 = R_3 = NH_2$) (Y. Makisumi, Chem. Pharmac. Bull. (Tokyo) 9, 802 (1961)).

It was surprisingly found that these new compounds have coronary artery dilating effects that have been favorable in animal experiments and that are superior to the known compounds. The tests were carried out on isolated mammal hearts following the method of Langendorff (Pflügers Archiv 61, 219 (1895) in the modification of Ryser and Willbrandt (Arch. int. pharmacodyn.) XCVI 131 (1953)). It turned out that the compounds 5-(β-hydroxyethylamino)-7-diethylamino-s-triazolo(1,5-a)pyrimidine and 5-furfurylamino-7-benzylamino-s-triazolo(1,5-a)pyrimidine have coronary vessel dilating effect that is 10-20 times that of euphyllin or theocor.

In accordance with the invention the new compounds are obtained if triazolo(1,5-a)pyrimidines of the general formula II



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in which either both residues R_5 and R_6 represent halogen atoms or one of the residues R_5 and R_6 is a free or alkylated mercapto group or an alkoxy group and the other is a halogen atom, R_2 and R_4 have the meanings given above, is reacted with a compound of the general formula R_3H or $R_3(CH_2)_nONa$ and the resulting s-triazolo(1,5-a)pyrimidine substituted in position 7 by R_3 is reacted with a compound of the general formula R_1H or $R_1(CH_2)_nONa$, in which R_1 has the meaning given above. In the halogen compounds that are used as starting compounds with this procedure chlorine preferably occurs as the halogen atom. The reaction is carried out in a substantially known way. If one starts with a substituted 5,7-dichloro-s-triazolo(1,5-a)pyrimidine, first the chlorine atom in position 7 is exchanged under mild reaction conditions, for Example at room temperature, after which the halogen atom in position 5 is replaced by an optionally substituted amino or basically substituted alkoxy group under more severe reaction conditions, for Example, at the boiling point of the solvent or under pressure. If more severe reaction conditions are used straight away, the halogen atoms in positions 5 and 7 are exchanged

in one operation. Preferably water, water-alcohol mixtures, alkanols, optionally toluene, dioxane or chloroform are used as solvents. Amines, triethylamine or alkali carbonates, which are used in an excess quantity, are utilized to bind the hydrohalic acid that may be released in the reaction. The reaction products are processed in the usual way by separating the end products from the halogen compounds that have formed and purifying them by recrystallization, distillation, sublimation or extraction.

If 5-halo-7-alkoxy(alkylmercapto)-s-triazolo(1,5-a)pyrimidines are used as starting compounds, these compounds are preferably reacted at the boiling point of the solvent, for example, ethanol, dioxane, with the amines of the formula R_3NH, which are used in an excess quantity. In this case alkylmercaptan or alcohols are split off. The end product remains in the solution and is purified as indicated above. The basically substituted alkoxy compounds are prepared by the reaction of the compounds of general formula II in which R_1 and R_3 mean halogen atoms, with the sodium compounds of the amino alcohols. The compounds that are obtained are purified as described above.

The substituted 5,7-dichloro-s-triazolo(1,5-a)pyrimidines that are required as starting products are prepared in the usual way by reacting the 5,7-dihydroxy compounds with phosphorus oxychloride, optionally in the presence of dimethylformamide or N,N-dimethylaniline. The 5-halo-7-alkoxy-s-triazolo(1,5-a)pyrimidines are obtained from the 5,7-dichloro compounds by a reaction with sodium alcoholate at low temperatures, while the 5-halo-7-alkylmercapto-s-triazolo(1,5-a)pyrimidines are obtained by the reaction of the 5,7-dichloro compounds with hydrogen sulfides followed by alkylation. The required substituted 5,7-dihydroxy-s-triazolo(1,5-a)pyrimidines, insofar as they are not known compounds, are obtained in the usual way by condensation of an optionally substituted 5-amino-1,2,4-triazolo with an optionally substituted malonic ester.

The resulting compounds can be converted to their salts by treatment with acids. The method in accordance with the invention is illustrated by means of the following examples:

Example 1

9.4 g 5,7-dichloro-s-triazolo(1,5-a)pyrimidine are slowly reacted with 7.5 g diethylamine in 100 cm^3 water. The batch is stirred for 2 h at room temperature, then 2 h at 70-80°C. Then it is cooled and acidified. It is filtered, made alkaline, and extracted with chloroform. The extract is dried, concentrated and extracted with gasoline. One obtains 10 g colorless crystals of 5-chloro-7-diethylamino-s-triazolo(1,5-a)pyrimidine, with a melting point of 111-112°C.

Example 2

5.7 g of the 5-chloro-7-diethylamino-s-triazolo(1,5-a)pyrimidine are dissolved in 50 cm^3 n-butanol, 6 g benzylamine are added, and the mixture is heated under reflux for 5 h. The hydrochloride precipitates out upon cooling. The filtrate is vacuum concentrated in a vacuum and taken up in water. The initially viscous mass crystallizes completely. The yield is 6 g. Recrystallized from ethyl acetate, the resulting 5-benzylamino-7-ethylamino-s-triazolo(1,5-a)pyrimidine melts at 146-147°C.

Example 3

10.7 g benzylamine are added at room temperature to a solution of 2.4 g 5,7-dichloro-s-triazolo(1,5-a)pyrimidine in 100 cm^3 ethanol and the mixture is stirred for another 2 h at this temperature and then the batch is heated to the boiling point for 2 h. Then it is vacuum dried, and the residue is mixed with water and crystallized. The yield is 12 g. The 5-chloro-7-benzylamino-s-triazolo(1,5-a)pyrimidine melts at 178-179°C, after recrystallization from ethanol.

Example 4

6.5 g 5-chloro-7-benzylamino-s-triazolo(1,5-a)pyrimidine are added to a mixture of 30 cm^3 butanol and 20 cm^3 diethylamine. The reaction mixture is held at reflux for 8 h. The alcohol is distilled out, the residue is taken up in water, made alkaline with sodium hydroxide, and shaken with chloroform. After driving off the chloroform there remains a slowly crystallizing residue. After recrystallization from ethyl acetate, one obtains 6.3 g 5-diethylamino-7-benzylamino-s-triazolo(1,5-a)pyrimidine, with a melting point of 125-126°C.

Example 5

6.2 g 5-chloro-7-furfurylamino-s-triazolo(1,5-a)pyrimidine are heated with 5.3 g diethanolamine and 50 cm^3 butanol for 5 h with stirring under reflux. The excess butanol is distilled out under vacuum, the residue is dissolved with acid in water, filtered, the filtrate is adjusted to pH 5 with a soda solution and the resulting crystalline precipitate is recrystallized from water. Yield: 6.2 g 5-[bis(β-hydroxyethyl)amino]-fufurylamino-s-triazolo(1,5-a)pyrimidine, m.p. 107°C.

Example 6

12.1 g β-phenylethylamine are slowly added by drops at room temperature to 9.4 g 5,7-dichloro-s-triazolo(1,5-a)pyrimidine dissolved in 150 cm^3 ethanol. After standing for 2 h at room temperature the mixture is heated at the reflux for 2 h. Ethanol is distilled out under a vacuum,

water is added, the crystallizate is suctioned out and recrystallized from ethanol. The yield is 14 g 5-chloro-7-(β-phenylethylamino)-s-triazolo(1,5-a)pyrimidine, m.p. 145-146°C.

Example 7

4.7 g 5,7-dichloro-s-triazolo(1,5-a)pyrimidine, 25 cm^3 abs. ethanol and 10 g diethylamine are heated to 100°C for 8 h in a bomb tube. The ethanol is distilled out and the residue is taken up in water. After alkalinization the mixture is extracted with chloroform, the solvent is distilled out, and the residue is distilled in a high vacuum. Yield: 4 g, $b.p._{0.2}$ 165-170°C.

Example 8

8.5 g piperidine are added to a suspension of 3.8 g 5,7-dichloro-s-triazolo(1,5-a)pyrimidine in water/isopropanol and the mixture is stirred for 3 h at room temperature, and then 3 h at the boiling point. It is concentrated under a vacuum, the residue is recrystallized from water/ethanol. One obtains 3.5 g 5,7-bis(piperidino)-s-triazolo(1,5-a)pyrimidine monohydrate, m.p. 79°C.

Example 9

3.6 g 2-ethyl-5,7-dichloro-s-triazolo(1,5-a)pyrimidine, 5 g diethylamine and 20 cm^3 ethanol are heated for 15 min at reflux. The crystallizate remaining after distilling out the solvent is extracted with gasoline. 3.5 g 2-ethyl-5-chloro-7-diethylamino-s-triazolo(1,5-a)pyrimidine with a melting point of 79-80°C are obtained.

Example 10

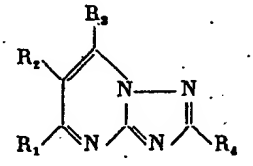
2.2 g 2-ethyl-5,7-dichloro-s-triazolo(1,5-a)pyrimidine, 20 cm^3 n-butanol and 7.5 g piperidine are heated for 3 h at boiling. The solvent is distilled out and the residue is extracted with gasoline. The yield is 2 g 2-ethyl-5,7-bis(piperidino)-s-triazolo(1,5-a)pyrimidine, m.p. 69°C.

Example 11

15 g piperidine are added to 4.9 g of 2,6-dis(ethyl-5,7-dichloro-s-triazolo(1,5-a)pyrimidine and heated at reflux for 3 h. The residue remaining after evaporating out the excess piperidine is extracted with gasoline, giving a yield of 4 g 2,6-dis(ethyl)-5,7-bis(piperidino)-s-triazolo(1,5-a)pyrimidine. The melting point of the hydrochloride of this compound is 165°C.

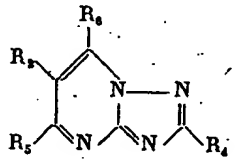
Claim

A method for producing s-triazolo(1,5-a)pyrimidines of the general formula I substituted in positions 5 and 7 by basic groups and their salts



(I)

in which R_2 and R_4 mean hydrogen atoms, alkyl residues of chain length C_1-C_4, halogen atoms or optionally nucleus-substituted aralkyl-aryl or heterocyclic residues, where R_2 and R_4 do not necessarily have to be the same, R_1 and R_3 represent free amino groups or amino groups substituted by the same or different residues, where these residues [can be] alkyl, cycloalkyl, alkenyl, hydroxyalkyl, alkylaminoalkyl, alkoxy groups, and also aryl or aralkyl groups that are optionally substituted or that optionally contain hetero atoms, also optionally substituted hydrazine [or] guanidino or basically substituted alkoxy residues with a normal or branched alkyl chain of 2-4 carbon atoms, in which the basic residue can carry the substituents indicated above, R_1 and R_3 do not have to be the same, which is characterized by the fact that a) triazolo(1,5-a)pyrimidines of general formula II, in which R_5 and R_6 stand for halogen atoms, mercapto, alkylmercapto or alkoxy groups, R_2 and R_4



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have the meanings given above, are reacted with amines of the general formula R_3H or R_1H or alcoholates of the general formula $R_3(CH_2)_nONa$ or $R_1(CH_2)_nONa$, in which n can take on values of 2, 3 and 4, and R_1 and R_4 have the meanings given above, in the presence or absence of solvents and in the presence of acid-binding agents like amines or alkali carbonates, or b) the reactions of the compounds of the general formula II in which R_5 and R_6 stand for a halogen atom are preferably carried out in water or water-alcohol mixtures, and the resulting bases are converted to their salts by means of acids.